REMARKS

Claims 22-37 are pending in the application. Applicants reserve the right to prosecute non-elected subject matter in subsequent divisional applications.

Amendment to the specification

The paragraph beginning at page 39, line 25 has been amended to clarify that Donor 4097 was a patient who had colon cancer derived from metastasis of gastric sarcoma. Support for this amendment can be found in the specification, for example, at page 11, lines 25-28, and in Table 5 which describe experiments performed on cancerous colon tissue samples from Donor 4097. In addition, the attention of the Examiner is directed to Exhibit A, which shows an entry from a proprietary Incyte Genomics database containing information regarding Donor 4097. No new matter is added to the specification by this amendment. Therefore, entry of the amendment is respectfully requested.

Comments regarding restriction requirement

Applicants affirm the election with traverse of Group I, which corresponds to newly added claims 24-28, 31, and 37 drawn to polynucleotides, and the election with traverse of SEQ ID NO:3 (encoding the polypeptide of SEQ ID NO:1). Newly added claims 24-28, 31, and 37 replace original claims 1-4 and 6-8, and are drawn to substantially the same invention, but are of a different scope.

Claims 29, 30 and 32-36 are "method of use" claims which depend from the elected product claims. Therefore, upon allowance of the elected product claims, it is believed that claims 29, 30 and 32-36 should be rejoined and considered in accordance with the Commissioner's Notice in the Official Gazette of March 26, entitled "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C.§ 103(b)."

Enablement Rejection under 35 U.S.C. §112, First Paragraph

Original claims 1-4 and 6-8, now replaced by new claims 24-28, 31, and 37, have been rejected under 35 U.S.C. §112, first paragraph, on the grounds that the specification allegedly does not provide an enabling disclosure commensurate in scope with the claims" (Office Action, page 2). In

particular, the Office Action alleges that "it would take undue experimentation to use the invention in colon cancer diagnosis." Applicants traverse the rejections for the reasons already made of record in the responses to the Office Actions of October 23, 2001 and June 4, 2002, the Declaration of Dr. Amy Lasek, and on the following grounds.

The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.

> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be take as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Applicants submit that the disclosure amply enables the claimed invention. It is undisputed that the claimed polypeptide, shown as SEQ ID NO:1 in the patent application and referred to as IP-1, shares 64% sequence identity over 475 amino acid residues with a rabbit intestinal protein (g1762) (Specification at page 11, lines 8-13). The reference of Boll et al., cited in the specification, discusses the rabbit intestinal protein (g1762) as potentially useful as a marker of intestinal development and differentiation (Specification at page 3, lines 11-22, and IDS reference #6). Moreover, the specification discloses that SEQ ID NO:1 is indeed an intestinal protein. Table 1 shows that SEQ ID NO:3, which encodes SEQ ID NO:1, is expressed predominantly in digestive system tissues, and Table 2, more specifically shows that SEQ ID NO:3 is expressed primarily in colon tissues (Table 2). The Examiner stresses the need for "age, sex matched normal controls" in order to validate the usefulness of a biomarker. Although the Examiner is correct that Table 2 shows expression of SEQ ID NO:3 in normal and diseased colon tissue from unmatched donors, the data do indicate that SEQ ID NO:3 is useful as a colon marker. Additional expression data for SEQ ID NO:3, including carefully "matched normal controls," are presented in Table 5.

The Patent Examiner does not dispute that the claimed polynucleotide can be used as a probe in cDNA microarrays and used in gene expression monitoring applications. Instead, the Patent Examiner contends that the claimed polynucleotide cannot be useful without precise knowledge of its biological function. Not so. SEQ ID NO:3 can be useful in toxicology testing, drug development and disease diagnosis through gene expression profiling in the absence of any knowledge as to the precise function of the protein encoded by it. The claimed invention is not some random sequence whose value as a probe is speculative or would require further research to determine.

Table 5 clearly shows that SEQ ID NO:3 is differentially expressed in association with colon cancer in some patients. Contrary to the Examiner's assertions, Table 5 presents microarray data from comparisons of carefully matched tissue samples. In every experiment, differential expression was calculated for a single donor from comparisons of cancerous colon tissue and non-cancerous colon tissue taken from that donor. The Examiner expresses confusion concerning whether Donor 4097 had colon cancer. Applicants wish to clarify that Donor 4097 was a patient suffering from both gastric cancer and colon cancer, and that Table 5 shows experimental data for cancerous colon tissue removed from that donor. The Examiner alleges that the microarray data presented in Table 5 show that changes in expression were less than 2-fold. This is also not true. As explained previously, Table 5 shows **log2 values** of the differential expression. The differences in expression in comparisons between matched cancerous and non-cancerous tissues ranged from about 2 to 5-fold.

Further, the Examiner suggests that SEQ ID NO:3 cannot be useful if "the expression is not specific to any specific colon disease" (Office Action, page 3). This is not true. Expression of SEQ ID NO:3 at some level in normal colon tissue as well as in diseased colon tissue does not prevent SEQ ID NO:3 from being useful for diagnosis of colon cancer. The data presented in Table 5 indicate that SEQ ID NO:3 may be useful in diagnosis of colon cancer based on the experimental results showing differential expression in comparisons of cancerous tissue and "normal" controls for donor-matched tissue samples. The Examiner alleges that differential expression may be indicative of some other disease such as, for example, ulcerative colitis or Crohn's disease based on the data shown in Table 2. Applicants contend that SEQ ID NO:3 as a colon marker may be useful in diagnosis of more than one type of colon disorder. Applicants are not suggesting that microarray analysis be the only form of disease diagnosis used in treating a patient. Rather, microarray analysis may be useful in supplementing

existing methods of diagnosis and treatment. In reality, an initial diagnosis of a suspected colon cancer would likely be made by other evaluations, such as tissue pathology, which would rule out other disease conditions. Microarray data may be used to assist diagnosis and to monitor differential expression of the polynucleotide during the course of drug therapy of an established colon cancer (Please see the enclosed references of Zhang et al. (2001) Proc. Natl. Acad. Sci. 98:6730-6735) and Jass (2002) Surg. Clin. North Am. 82:891-904 for a discussion of the use of microarray technology in the diagnosis and treatment of colon cancer).

The microarray methods used to produce the data in Table 5 are described in the specification, for example, at pages 36-39 and in the Declaration of Dr. Amy Lasek and could be used by one of skill in the art without undue experimentation. Therefore, one skilled in the art would readily be able to conduct similar experiments using biopsied colon tissues from patients suspected of having colon cancer with the expectation that at least a 2-fold reduction in expression of SEQ ID NO:3 in the suspected cancerous colon tissue compared to the normal tissue would be indicative of colon cancer.

The Office Action cites various articles that supposedly discount the use of microarray data for disease diagnosis (Office Action, pages 3-4). For example, the Examiner cites the article of Marx (2000; Science 289:1670-1672) to suggest that "lack of standardization" makes it difficult to assess the quality of microarray data and to compare results from different labs. Here, the Examiner has misleadingly focused on a few sentences in an article that discusses the value of microarray analysis for diagnosis and treatment of cancer. The Marx article describes the use of microarray technology for identification of specific genes, whose expression is turned up or down in association with cancer, that may be potential drug targets. The article describes using microarray analysis for monitoring changes in gene expression patterns associated with different types of cancer to improve diagnosis and prediction of clinical outcome and for conducting toxicity studies to determine how cancer cells respond to chemotherapeutic agents. What the Marx article does not suggest is that microarray data is useless because of some technical difficulties in comparing results among labs. On the contrary, the Marx article extols the development of microarray technology and its usefulness in cancer diagnosis. The main thrust of the article is the following:

> Now researchers have a powerful new tool that not only should help them sort out the differences that define the many types of cancer, but also should help identify new targets for therapeutic drugs. (Marx supra, p.1670)

Next, the Examiner insists that validation of the usefulness of a biomarker requires analysis of a large set of clinical samples, and therefore, undue experimentation would be required to prove that SEQ ID NO:3 would be useful in cancer diagnosis. The Examiner cites the Tockman et al. article (1992; Cancer Res. 52:2711s-2718s), in support of the argument that "prior to successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials" (Office Action, page 4). Such a position is believed to represent a misapplication of the law.

The Examiner demands further research to establish that the use of SEQ ID NO:3 as a cancer biomarker would be credible; therefore, this rejection is tantamount to a utility rejection under 35 U.S.C. §101. As set forth in the M.P.E.P. § 2107.03:

> There is no predetermined amount of character of evidence that must be provided by an applicant to support an asserted utility, therapeutic or otherwise.... Furthermore, the applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." *In re Irons*, '340 F.2d 974, 978, 144 USPQ 351,354 (CCPA 1965). Nor must an applicant provide evidence such that it established an asserted utility as a matter of statistical certainty.
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> * * *
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> Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials. There is no decisional law that requires an applicant to provide data from human clinical trials to establish utility for an invention related to treatment of human disorders... **(human clinical data is not required to demonstrate the utility of the claimed invention, even though those skilled in the art might not accept other evidence to establish the efficacy of the claimed therapeutic compositions and the operativeness of the claimed methods of treating humans).** [Emphasis added.]

Applicants have presented evidence that the claimed polynucleotide is useful for diagnosis of colon cancer. Contrary to the Examiner's assertions, wide population studies are not required by law to establish beyond all doubt that the claimed polynucleotide can be useful for diagnosis of a particular stage of colon cancer. Table 5 provides sufficient examples of the reduction of expression of the

polynucleotide encoding SEQ ID NO:1 in association with colon cancer by comparing for each donor that was tested matched tumor and normal colon tissue, as would likely be done in an actual diagnosis.

Furthermore, at the time the application was filed, microarray technology and the methods described in the application were known to those of skill in the art, and a number of publications had confirmed and further established the utility of cDNA microarrays in a wide range of drug development gene expression monitoring applications. The Brown and Shalon U.S. Patent No. 5,807,522 (the Brown '522 patent), which issued from a patent application filed in June 1995 and was effectively published on December 29, 1995 as a result of the publication of a PCT counterpart application, shows that the Patent Office recognizes the patentable utility of the cDNA technology developed in the early to mid-1990s. The Brown '522 patent further teaches that:

> "[m]icroarrays of immobilized nucleic acid sequences prepared in accordance with the invention" can be used in "numerous" genetic applications, including "monitoring of gene expression" applications (at col. 14, lines 36-42). The Brown '522 patent teaches (a) monitoring gene expression (i) in different tissue types, (ii) in different disease states, and (iii) in response to different drugs, and (b) that arrays disclosed therein may be used in toxicology studies (at col. 15, lines 13-18 and 52-58 and col. 18, lines 25-30).

Literature reviews published before the filing of the application describing the state of the art further confirm the claimed invention's utility. Rockett, et al. confirm, for example, that the claimed invention is useful for differential expression analysis regardless of how expression is regulated:

> Despite the development of multiple technological advances which have recently brought the field of gene expression profiling to the forefront of molecular analysis, recognition of the importance of differential gene expression and characterization of differentially expressed genes has existed for many years.
>
> * * *
>
> Although differential expression technologies are applicable to a broad range of models, perhaps their most important advantage is that, in most cases, absolutely no prior knowledge of the specific genes which are up– or down-regulated is required.
>
> * * *
>
> Whereas it would be informative to know the identity and functionality of all genes up/down regulated by . . . toxicants, this would appear a longer term goal . . . . However, the current use of gene profiling yields a *pattern* of gene changes for a

> xenobiotic of unknown toxicity which may be matched to that of well characterized toxins, thus alerting the toxicologist to possible *in vivo* similarities between the unknown and the standard, thereby providing a platform for more extensive toxicological examination. (emphasis added)

Rockett et al., Differential gene expression in drug metabolism and toxicology: practicalities, problems and potential, 29 Xenobiotica No. 7, 655 (1999).

Lashkari, et al. state explicitly that sequences that are merely "predicted" to be expressed (predicted Open Reading Frames, or ORFs) – the claimed invention in fact is known to be expressed – have numerous uses:

> Efforts have been directed toward the amplification of each predicted ORF or any other region of the genome ranging from a few base pairs to several kilobase pairs. There are many uses for these amplicons– they can be cloned into standard vectors or specialized expression vectors, or can be cloned into other specialized vectors such as those used for two-hybrid analysis. The amplicons can also be used directly by, for example, arraying onto glass for expression analysis, for DNA binding assays, or for any direct DNA assay.

Lashkari, et al., Whole genome analysis: Experimental access to all genome sequenced segments through larger-scale efficient oligonucleotide synthesis and PCR, 94 Proc. Nat. Acad. Sci. 8945 (Aug. 1997) (emphasis added).

The technologies made possible by expression profiling and the DNA tools upon which they rely are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment.

Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett, et al., *supra*:

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs.

To the same effect are several other scientific publications, including Emile F. Nuwaysir, et al., Microarrays and Toxicology: The Advent of Toxicogenomics, 24 Molecular Carcinogenesis 153

(1999); Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, 112-13 Toxicology Letters 467 (2000).

Nucleic acids useful for measuring the expression of whole classes of genes are routinely incorporated for use in toxicology testing. Nuwaysir et al. describes, for example, a Human ToxChip comprising 2089 human clones, which were selected

> for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. Included on this list are DNA replication and repair genes, apoptosis genes, and genes responsive to PAHs and dioxin-like compounds, peroxisome proliferators, estrogenic compounds, and oxidant stress. Some of the other categories of genes include transcription factors, oncogenes, tumor suppressor genes, cyclins, kinases, phosphatases, cell adhesion and motility genes, and homeobox genes. Also included in this group are 84 housekeeping genes, whose hybridization intensity is averaged and used for signal normalization of the other genes on the chip.

See also Table 1 of Nuwaysir et al. (listing additional classes of genes deemed to be of special interest in making a human toxicology microarray).

The more genes that are available for use in toxicology testing, the more powerful the technique. "Arrays are at their most powerful when they contain the entire genome of the species they are being used to study." John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology, 107 Environ. Health Perspec.681, No. 8 (1999). Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator on the Nuwaysir paper, Dr. Cynthia Afshari, to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding, indicating that even the expression of carefully selected control genes can be altered. Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangiers disease. This discovery took place over a matter of only a few weeks, due to the

power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility."

Envirotech Corp. v. Al George, Inc., 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. *See Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a "nebulous expression" such as "biological activity" or "biological properties" that does not convey meaningful information about the utility of what is being claimed. *Cross* v. *Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Office bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Id.* To do so, the Patent Office must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

There is no dispute that the claimed invention is in fact a useful tool in cDNA microarrays used to perform gene expression analysis. That is sufficient to establish utility for the claimed polynucleotide A person skilled in the art would have understood the claimed polynucleotide to be useful for a numbe

of gene expression monitoring applications, *e.g.*, as a highly specific probe for the expression of that specific polynucleotide in connection with the development of drugs and the monitoring of the activity of such drugs. A cDNA microarray that contained the SEQ ID NO:1-encoding polynucleotide would be a more useful tool than a cDNA microarray that did not contain the polynucleotide in connection with conducting gene expression monitoring studies on proposed (or actual) drugs to treat colon cancer for such purposes as evaluating their efficacy and toxicity.

Given the fact that the claimed polynucleotide is known to be expressed, its utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight. This use as a measuring tool, regardless of how the expression level data ultimately would be used by a person of ordinary skill in the art, by itself demonstrates that the claimed invention provides an identifiable, real-world benefit that meets the utility requirement. *Raytheon* v. *Roper*, 724 F.2d 951, (Fed. Cir. 1983) (claimed invention need only meet one of its stated objectives to be useful); *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999) (how the invention works is irrelevant to utility); MPEP § 2107 ("Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific, and unquestionable utility (e.g., they are useful in analyzing compounds)" (emphasis added)).

Though Applicants need not so prove to demonstrate utility, there can be no reasonable dispute that persons of ordinary skill in the art have numerous uses for information about relative gene expression including, for example, understanding the effects of a potential drug for treating colon cancer or other colon disorders such as Crohn's disease and ulcerative colitis. Because the patent application states explicitly that the claimed polynucleotide is known to be expressed in colon tissues (Specification at Tables 2 and 5), there can be no reasonable dispute that a person of ordinary skill in the art could put the claimed invention to such use. In other words, the person of ordinary skill in the art can derive more information about a potential colon disorder and colon cancer drug candidate or potential toxin with the claimed invention than without it.

There is, in fact, no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. Indeed, "real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12

USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing all expressed genes (along with the polypeptide translations of those genes), in particular genes having medical and pharmaceutical significance such as the instant sequence. (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Applicants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the claimed sequence and millions of other sequences throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

Both Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven to be valuable in, for example, the identification and development of drug candidates. As Incyte adds information to its databases, including the information that can be generated only as a result of Incyte's discovery of the claimed polynucleotides and use of these polynucleotides on cDNA microarrays, the databases become even more powerful tools. Thus the claimed invention adds more than incremental benefit to the drug discovery and development process.

According to the Examiner, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed invention either by itself or in a cDNA microarray to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. The Examiner would require, in addition, that the applicant provide a specific and substantial interpretation of the results generated in any given expression analysis.

It may be that specific and substantial interpretations and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is not, as the Examiner would have it, whether it is known how or why the invention works, *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an "identifiable benefit" in presently available form. *Juicy Whip Inc.* v. *Orange Bang Inc.*, 185 F.3d

1364, 1366 (Fed. Cir. 1999). If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt that the present invention meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called "throwaway" utilities that are not directed to a person of ordinary skill in the art at all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function or role of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged so much (66 F.R. at 1095):

> [T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, *e.g.*, it hybridizes near a disease-associated gene or it has gene-regulating activity.

By implicitly requiring knowledge of biological function for any claimed nucleic acid, the Examiner has, contrary to law, elevated what is at most an evidentiary factor into an absolute requirement of utility. Rather than looking to the biological role or function of the claimed invention, the Examiner should have looked first to the benefits it is alleged to provide.

As used in toxicology testing, drug discovery, and disease diagnosis, the claimed invention has a beneficial use in research other than studying the claimed invention or its protein products. It is a tool, rather than an object, of research. The data generated in gene expression monitoring using the claimed invention as a tool is **not** used merely to study the claimed polynucleotide itself, but rather to study properties of tissues, cells, and potential drug candidates and toxins. Without the claimed invention, the information regarding the properties of tissues, cells, drug candidates and toxins is less complete.

The claimed invention has numerous additional uses as a research tool, each of which alone is a "substantial utility." These include uses such as diagnostic assays (e.g., pages 21-22), chromosomal markers (e.g., page 17), and ligand screening assays (e.g., page 24-25). To the extent the rejection of

the patented invention under 35 U.S.C. § 112, first paragraph, is based on the improper rejection for lack of utility under 35 U.S.C. § 101, it must be reversed.

The utilities and methods of use described above for SEQ ID NO:3 would also apply to the claimed variants of SEQ ID NO:3. Applicants also respectfully point out that the claims of the instant application are drawn to naturally-occurring variants. Thus, it is not necessary to screen every conceivable variant which might be made using recombinant methods, as all that is claimed are those variant sequences which are found in nature. Given the sequences of SEQ ID NO:1 and SEQ ID NO:3, one of ordinary skill in the art could readily identify naturally occurring variants having at least 90% identity, using well known methods of sequence analysis, without any undue experimentation.

Applicants are not claiming all possible variant polynucleotides, including the vast majority of useless theoretical molecules not occurring in nature, and thus not pre-selected by nature to be useful. Through the process of natural selection, nature will have determined the appropriate polynucleotide sequences. Members of the claimed genus of variants may include, for example, mutant alleles associated with diseases, or single nucleotide polymorphisms (SNPs). Members of the claimed genus of variants may be useful even if they encode defective IP-1 polypeptides. For example, the variant polynucleotides could be used for the detection of sequences related to IP-1 (see the specification at pages 14 and 16-17) including IP-1 variants that may be associated with disease states, such as the diseases listed on page 21, lines 12-13, of the specification. See the specification at, for example, pages 21-22 for disclosure of how to use the claimed sequences in diagnostic assays.

The identification of relevant polynucleotides could be performed by hybridization and/or PCR techniques that were well-known to those skilled in the art at the time the subject application was filed and/or described throughout the specification of the instant application (for example, pages 16-17 and 34-37). One skilled in the art need not make and test vast numbers of polynucleotides that are based on the polynucleotide sequence of SEQ ID NO:3. Instead, one skilled in the art need only screen a cDNA library or use appropriate PCR conditions to identify relevant polynucleotides/polypeptides that already exist in nature. Methods of expression of recombinant polynucleotides encoding IP-1 or variants having at least 90% sequence identity to SEQ ID NO:1 and methods of purification of the polypeptides so expressed are described in the specification, for example, at pages 17-19. Given this guidance, one of ordinary skill in the art would readily understand how to select and screen

polynucleotide variants of SEQ ID NO:3 without any undue experimentation. The skilled artisan would also know how to use the claimed variants, for example, in expression profiling, disease diagnosis, or detection of related sequences as discussed above.

For at least the above reasons, withdrawal of the enablement rejections of claims 24-28, 31, and 37 under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Rejections under 35 U.S.C. § 102

Original claims 1, 3, 4 and 6-8, now replaced by new claims 24, 27, 28, and 37 have been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by either the reference of Boll et al. (1993) J. Biol. Chem. 268:12901-12911) or NCBI accession number AI833131. In particular, the Office Action alleges that the references of Boll et al. and AI833131 anticipate the claimed polynucleotides encoding antigenic epitopes of SEQ ID NO:1 and a fragment specified in original claim 3 (Office Action, pages 6 and 7).

Claim 22(c) (from which claim 24 depends) recites:

> an immunogenic portion of a polypeptide comprising the amino acid sequence of SEQ ID NO:1 selected from the group consisting of:
> 1) an immunogenic portion of a polypeptide consisting of the sequence of SEQ ID NO:1 from residue 66 to residue 90,
> 2) an immunogenic portion of a polypeptide consisting of the sequence of SEQ ID NO:1 from residue 120 to residue 141,
> 3) an immunogenic portion of a polypeptide consisting of the sequence of SEQ ID NO:1 from residue 234 to residue 245, and
> 4) an immunogenic portion of a polypeptide consisting of the sequence of SEQ ID NO:1 from residue 351 to residue 359.

The specification describes portions of SEQ ID NO:1 containing antigenic epitopes at page 12, lines 13-14 and at page 40, lines 17-22. The specification, at page 9, lines 29-30, defines a "portion" of a protein as "any part of a protein used for any purpose; but especially, to an epitope for the screening of ligands or for the production of antibodies." Applicants submit that the polynucleotides encoding immunogenic portions of SEQ ID NO:1 as now claimed are not anticipated by either the reference of Boll et al. or AI833131.

With respect to the additional polynucleotide fragments that are claimed, claim 37 as currently pending recites:

> 37. A fragment of a polynucleotide comprising the sequence of SEQ ID NO:3 selected from the group consisting of:
> a) a fragment of a polynucleotide consisting of the sequence of SEQ ID NO:3 from nucleotide 170 to nucleotide 220, and
> b) a fragment of a polynucleotide consisting of the sequence of SEQ ID NO:3 from nucleotide 1015 to nucleotide 1055.

Applicants submit that none of these polynucleotide fragments as currently claimed are anticipated by either reference.

For at least these reasons, withdrawal of the rejections under 35 U.S.C. § 102(b) is respectfully requested.

Rejections under 35 U.S.C. § 112, second paragraph

Original claim 3, now replaced by claim 37, was rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite. Claim 37 as currently pending recites:

> 37. A fragment of a polynucleotide comprising the sequence of SEQ ID NO:3 selected from the group consisting of:
> a) a fragment of a polynucleotide consisting of the sequence of SEQ ID NO:3 from nucleotide 170 to nucleotide 220, and
> b) a fragment of a polynucleotide consisting of the sequence of SEQ ID NO:3 from nucleotide 1015 to nucleotide 1055.

The limitations of the claimed fragments are now clear; therefore, withdrawal of the rejection under 35 U.S.C. § 112, second paragraph is respectfully requested.

Written description rejections under 35 U.S.C. § 112, first paragraph

Original claims 1, 3, 4, and 6-8, now replaced by 24, 25, 27, 28, 31, and 37 have been rejected under the first paragraph of 35 U.S.C. 112 for alleged lack of an adequate written description. This rejection is respectfully traversed.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first

paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics[42] which provide evidence that applicant was in possession of the claimed invention,[43] i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.[44] What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.[45] If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.[46]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

SEQ ID NO:1 and SEQ ID NO:3 are specifically disclosed in the application (see, for example, pages 11-12). Variants of SEQ ID NO:3 are described, for example, at pages 13-14. Incyte clones in which the nucleic acids encoding the human IP-1 were first identified and libraries from which those clones were isolated are described, for example, at page 11, lines 14-19 and page 28, lines 28-30 of the Specification. Chemical and structural features of SEQ ID NO:1 are described, for example, on page 12, lines 1-16. Given SEQ ID NO:1 and SEQ ID NO:3, one of ordinary skill in the art would recognize naturally-occurring variants of SEQ ID NO:1 or SEQ ID NO:3 having 90% sequence identity to SEQ ID NO:1 or SEQ ID NO:3. Accordingly, the Specification provides an adequate written description of the recited polynucleotide sequences.

A. The Specification provides an adequate written description of the claimed "variants" of SEQ ID NO:3.

The Office Action has further asserted that the claims are not supported by an adequate written description because "[s]ince the genus includes a large number of unpredictable species, possession of only one species is not seen as sufficient to reasonably convey possession of the entire genus" (Office Action, page 7).

Such a position is believed to present a misapplication of the law.

1. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. §112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polynucleotides in terms of chemical structure, rather than on functional characteristics. For example, the "variant language" of independent claim 31 recites chemical structure to define the claimed genus:

> 31. An isolated polynucleotide selected from the group consisting of: ...
> b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to a polynucleotide sequence of SEQ ID NO:3...

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:3. In the present case, there is no reliance merely on a description of functional characteristics of the polynucleotides recited by the claims. In fact, there is no recitation of functional characteristics. Moreover, if such functional recitations were included, it would add to the structural characterization of the recited polynucleotides. The polynucleotides defined in the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base its written description inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis of the present

claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*

2. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant." Available evidence illustrates that the claimed genus is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

The present application is directed, *inter alia*, to intestinal proteins related to the amino acid sequence of SEQ ID NO:1. In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as intestinal proteins and which have as little as 40% identity over at least 70 residues to SEQ ID NO:1. The "variant language" of the present claims recites, for example, polynucleotides encoding "a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1" (note that SEQ ID NO:1 has 475 amino acid residues). This variation is far less than that of all potential intestinal proteins related to SEQ ID NO:1, i.e., those intestinal proteins having as little as 40% identity over at least 70 residues to SEQ ID NO:1.

3. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. §112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an

Israeli application filed on November 21, 1979. Thus, the written description inquiry in those case was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology.

The present application has a priority date of December 4, 2000. Much has happened in the development of recombinant DNA technology in the 23 or more years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:1 and SEQ ID NO:3, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polynucleotide variants at the time of filing of this application.

4. Summary

The Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1 or SEQ ID NO:3. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polynucleotides defined by the present claims is adequately described, as evidenced by Brenner et al and consideration of the claims of the '740 patent involved in *Lilly*. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Attorney at (650) 855-0555.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. 09-0108.

Respectfully submitted,
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Date: February 27, 2003

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

The paragraph beginning at line 25 of page 39 has been amended as follows:

Matched normal colon and cancerous colon or colon polyp tissue samples were provided by the Huntsman Cancer Institute, (Salt Lake City, UT). Donor 4097 is a 48 year-old woman, diagnosed with gastric sarcoma and associated metastatic colon cancer. Donor 3649 is an 86 year-old individual, sex unknown, diagnosed with an invasive, well-differentiated adenocarcinoma. Donor 3647 is an 83 year-old individual, sex unknown, diagnosed with an invasive, moderately well-differentiated adenocarcinoma with [metastases] metastasis to the lymph nodes. Donor 3839 is a 60 year-old individual, sex unknown, diagnosed with colon cancer. Comparisons were done with matched normal and tumor or polyp tissue from the same donor. Donor 3983 is a 23 year-old individual, sex unknown, diagnosed with a polyp from adenomatous polyposis coli and with moderately differentiated adenocarcinoma that had metastasized to the lymph nodes.

IN THE CLAIMS:

Claims 1-4 and 6-21 have been canceled.

Claims 22-37 have been added.